REVISION 03 04/30/93

OPI: S&T/REPD

UNIDENTIFIED ANALYTICAL RESPONSES (UARs)

I. PURPOSE

This directive prescribes FSIS's policy for monitoring, identifying and reporting of UARs that occur in the residue program.

II. CANCELLATION

FSIS Directive 10,130.1, Rev. 2, dated 5-22-90.

III. REASONS FOR REISSUANCE

A. This revision expands the previous UAR directive to all residue analyses carried out by the TSLs or accredited laboratories. Furthermore, this directive places additional responsibility at the laboratory level for deciding if a UAR should be further investigated.

B. Paragraph IX. has been added to provide guidelines for the disposition of a product that contains a UAR.

C. The reporting requirement for the UAR Committee has been changed from monthly to quarterly because fewer UARs are currently being seen than in past years.

D. The names of certain program areas, as well as the analytical responsibilities of the TSLs, have changed subsequent to the 1990 directive. Further, the reference to the Western Laboratory in the directive of 1990 is no longer appropriate.

E. Because of the extensive changes to this directive, it has been rewritten in its entirety.

IV. REFERENCE

Analytical Chemistry Laboratory Guidebook - Winter 1991

V. ABBREVIATIONS

The following abbreviations are used in this directive:

CD	Chemistry Division
CES	Compound Evaluation System
IO	Inspection Operations
MARCIS	Microbiological and Residue Computer Information System
REPD	Residue Evaluation and Planning Division
ROS	Residue Operations Staff
S&T	Science and Technology

TSL Technical Services Laboratory
UAR(s) Unidentified Analytical Response(s)
UMA UAR Method Addendum

VI. POLICY

This directive identifies FSIS's system for monitoring UARs. The TSLs will report UARs as they are found in official samples to the Chief, Evaluation Branch, REPD, and the Director, CD, by entering the appropriate data into the MARCIS. The TSLs, REPD, and CD will evaluate UAR data for frequency of occurrence, product type, geographical source, Relative Concentration or any other factor which may determine the reasons for unknown detector responses. Additional sampling may be carried out by the Epidemiology and Emergency Programs Staff, IO, and further analyses may be performed if data evaluations indicate that they are necessary. When the identity of a UAR is determined, a CES evaluation of the compound or another means of assessing risk may be undertaken.

VII. DEFINITIONS

A. UAR. A UAR is an analytical response caused by a compound with chromatographic properties different from those of known reference standards and reagents; this can include endogenous components from tissue matrices. The majority of these responses are insignificant and vary among different chemical methodologies and tissue matrices.

B. UAR Committee. A committee at a TSL that is responsible for reviewing UAR data and making recommendations to REPD on continued work on the UAR. The committee will include the analyst, the supervisor for the laboratory section responsible for that method and the Chemist-in-Charge for Regulatory Chemistry.

VIII. EVALUATION PROCEDURES AND RESPONSIBILITIES

This paragraph describes the general procedures to be used by S&T personnel to evaluate and report UARs.

A. Recognition and Evaluation of UARs.

1. The individual TSL UAR committees will evaluate available information for each UAR finding and make recommendations to REPD and other interested divisions. In making the decision to pursue identification of the UAR, the UAR committee will follow guidelines specified in the Analytical Chemistry Laboratory Guidebook for that specific method. Each set of guidelines will be termed a "UAR method addendum" and will appear in the Guidebook as an attachment to the published method.

2. UMAs will be developed as needed for methods that are in current use in the National Residue Program. Each UMA will be

written by the TSL that performs the method in consultation with the Quality Systems Branch, CD. Each UMA will contain specific procedures for entering data into MARCIS. The general format each UMA will follow is specified in Paragraph XI. of this directive.

3. It is expected that appended UMAs to each in-use Guidebook method will not be available until July 1994. Therefore, until a UMA has been developed for a method, the following general guidelines will be employed to determine if it is justified to expend resources to identify a UAR. The TSL will do the following:

a. Proceed with identification only if the instrument response peak is of significant size; 3x the Lowest Reliable Quantitation of the method's reference compound is recommended as a general guideline. Determine the Relative Retention Time or Relative Retardation Factor and, where feasible, the Relative Concentration.

b. Use appropriate analytical methods (this will typically be mass spectrometry) to determine if the UAR is likely to correspond to a compound in the same class as that for which the method is designed. For example, if a UAR is found in a sulfonamide method, attempt to determine if the UAR is likely to be a sulfonamide.

c. If mass spectrometry, or some other informative analytical method, indicates that the compound appears to belong to the same class as that for which the method is designed, attempts will continue to be made to identify the compound. If the compound does not appear to belong to the same class as that for which the method is designed, significant additional resources should not be expended to attempt identification unless the compound appears to contain a halogen, aromatic amine or aromatic nitro group. Resources will not be expended to identify the compound if there is good reason to believe it is endogenous. If a compound is present in virtually all samples analyzed from a variety of sources, then it is likely to be endogenous. In a new method, at least 300 samples, from a variety of sources, should be analyzed before making a judgment that a compound is endogenous.

d. Following consultation with the TSL, REPD will recommend whether further identification of the UAR should be conducted by either the TSL, the Food and Drug Administration, or an academic or private laboratory working under government contract. REPD may also recommend that no further work be conducted to identify the UAR.

B. UAR Data Entry, Report Generation and Report Distribution.

1. After the TSL UAR committee agrees that the response is a UAR, the TSL should telecopy a completed copy of the agency sample form to the Chief, Evaluation Branch, REPD, and the Director, CD. When available, forward a copy of the completed analysis, all reports and information, including mass spectral data, to the above individuals by the next working day.

2. REPD and the Statistics and Data Systems Division are responsible for jointly reviewing the UAR data in MARCIS on a quarterly basis. The information in MARCIS will contain the following:

a. Relative Retention Time, Relative Retardation Factor and Relative Concentration (relative to the compound of interest on a method-specific basis), and Electron Impact Mass Spectrometry and Chemical Ionization Mass Spectrometry data, if applicable.

b. Species or product type.

c. Laboratory where analyzed.

d. Geographic area or county (identify imports in MARCIS).

e. Test method used (add to comment section in MARCIS).

f. Form number.

g. Internal laboratory sample number.

h. Identity of the UAR, when determined.

3. International Programs and Residue Operations Staff, IO, will receive a quarterly printout of the UAR data in MARCIS summarizing outstanding UARs.

C. Custody of Data and Samples. The TSLs will be responsible for the following activities:

1. Maintaining properly labeled chromatogram(s), mass spectrogram(s) and UAR data profiles of the sample analysis in the laboratory files.

2. Maintaining a properly labeled tissue sample in frozen storage for not less than 6 months.

D. UAR Quarterly Evaluation. REPD, CD, and the TSLs will jointly evaluate the UAR data quarterly and make either of the following recommendations to the Deputy Administrator, S&T:

1. Further analytical work should be conducted in a TSL on samples exhibiting similar data profiles to provide specific

chemical identification for recurring UARs, or

2. Further analytical work should be contracted with the Food and Drug Administration or an academic or private laboratory working under government contract.

E. Program Action. Once a UAR has been identified, the following actions may be initiated for future regulatory consideration:

1. A CES assessment by REPD.

2. A toxicologic evaluation by REPD.

3. An analytical method evaluation by CD.

4. An epidemiologic investigation by the Epidemiology and Emergency Programs Staff, IO.

5. Use of resources from other public health organizations for compound assessment.

IX. DISPOSITION OF A PRODUCT WHICH CONTAINS A UAR

If a product is being held pending laboratory analysis and a UAR is found but not identified and the product is not otherwise condemned, the following procedure should be followed:

A. The TSL will notify the Regional Residue Staff Officer of this situation within the established laboratory analysis turnaround time.

B. The Regional Residue Officer will consult with ROS regarding the disposition of this product.

X. ANALYSIS AND REPORTING PROCEDURES OF UARs BY AN FSIS CONTRACT LABORATORY

When an FSIS contract laboratory detects a UAR, the laboratory will forward all relevant information and a portion of the sample to the TSL for which the contract laboratory was performing the analysis.

XI. GENERAL FORMAT FOR THE UMA

Each UMA will be specific for a given method and will address method characteristics and the significance of the UAR.

A. The first section of the UMA will evaluate method characteristics, including:

1. Cleanup specificity,

2. Detection specificity,

3. Portion of the chromatogram that it is relevant to examine (isolation of the questionable area),

4. Special considerations for tissue, species, and product type, and

5. Method status (e.g., is the method validated).

B. The second section of the UMA will evaluate the UAR itself. The following criteria should be used to assess the significance of the UAR:

1. Peak response size,

2. Peak location, and

3. Frequency of occurrence.

C. Routine analytical procedures to be followed when a significant UAR is found:

1. Reinject or reanalyze the sample.

2. The TSL UAR committee will review and recommend analytical follow-up (e.g., mass spectrometry, atomic emission spectroscopy, nuclear magnetic resonance, or analysis on a second chromatography column).

D. Reporting procedures.

1. Appropriate MARCIS code numbers will be contained in each addendum.

2. TSL UAR committee will report findings in MARCIS to REPD.

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